Editorial Articles

A practical approach to the prevention of miscarriage: part 3 – passive immunotherapy

J.H. Check

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, NJ (USA)

Summary

Purpose: To evaluate the efficacy of passive immunotherapy in preventing miscarriage. *Methods:* Studies both pro and con concerning intravenous immunoglobulin therapy (IVIG) in preventing miscarriage were evaluated. A new therapy of IV intralipid infusion is also reviewed. *Results:* Intravenous immunoglobulin therapy may be effective but it is necessary to use it prior to conception and monthly thereafter. Some brands are more potent than others. The data concerning intralipid IV infusion involves only small case series but the results from one study were encouraging though we could not personally substantiate these findings. *Conclusions:* Intravenous immunoglobulin therapy is very expensive. In the author's opinion there are no immunological studies that can determine if a woman needs immune suppression. The best way to decide is the history – the more miscarriages without any other identifiable cause the more likely passive immunotherapy may be helpful. If intralipid proves as efficacious as IVIG it will be a lot less expensive.

Key words: Intravenous immunoglobulin; Intralipid infusion; Recurrent pregnancy loss; Natural killer cells.

Passive immunotherapy with intravenous immunoglobulins

We take the Hippocratic oath to do no harm. Though intravenous immunoglobulin (IVIG) because of sterilization procedures is generally considered safe from an infectious standpoint its biggest downfall is its expense. It is expensive to use on a one-time basis and for optimal success the recommendation is to use it every month. Even more "financially" harmful is that it should be used prior to conception for maximum effectiveness and thus IVIG could be wasted for three to eight months before conception occurs assuming that it even has benefit in preventing another miscarriage [1-5].

The theoretical mechanism by which IVIG may prevent miscarriage includes decreasing the killing activity of natural killer (NK) cells [6]. As mentioned in the editorial on active immunotherapy with lymphocytes, the beneficial effect of IVIG in this regard may be from the leakage of CD 200 molecules from lymphocytes. These particles may be responsible for the induction of progesterone receptors on gamma/delta T cells which allows the expression of a 34 kDA protein, the progesterone induced blocking factor (PIBF), which is ultimately responsible for suppression of NK cell activity [7, 8]. The use of IVIG may also prevent miscarriage by increasing the activity of suppressor T cells [6]. Thus if in some cases the problem is more related to increased T cell activity, IVIG could help in this manner.

Thus lymphocyte immunotherapy, as discussed in the first part of "A practical approach to the prevention of miscarriage: Part 2 – active immunotherapy", is believed to mainly inhibit NK cell mediated fetal damage. However, if the problem is related to activated T cell attack through depressed activity of suppressor T cells, or an increase in thymic helper (TH)-1 cytokines, IVIG may be more effective than lymphocyte immunotherapy. My own bias is that more often the problem is related to NK cell attack and frequently all one needs to do is add extra progesterone [8].

For those women where the use of extra progesterone still allows the miscarriage of a chromosomally normal fetus, I would next try active immunotherapy with lymphocyte immunotherapy instead of IVIG because the mechanism may involve specific localized suppression of NK cell activity at the maternal-fetal interface. In contrast, passive IVIG may cause more of a generalized NK cell suppression rather than local. Nevertheless, if the mechanism in suppressing NK cells does involve the high concentration of CD 200 molecules, then it is possible that it may exert a generalized decrease in cytotoxic T cell activity but work in a similar manner as lymphocyte immunotherapy when it comes to suppressing NK cell activity. The possibility exists that if the IVIG contains these CD200 molecules it could act as an active immunotherapy agent with possible induction of progesterone receptors on gamma/delta T cells to allow better expression of PIBF when there is exposure to adequate progesterone. Thus I believe that studies involving the efficacy of either lymphocyte immunotherapy or IVIG in preventing miscarriage should be performed in the setting of extra progesterone support.

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To my knowledge there are no randomized studies comparing the efficacy of lymphocyte immunotherapy to IVIG in preventing miscarriage or increasing IVF success. However, since in my opinion there are no tests at present that can tell who needs immune therapy, or when cytotoxic T cell rather than NK cell suppression will be needed, my preferences would be to use lymphocyte immunotherapy because it is so much less expensive than IVIG therapy. My preference would be to first treat a woman with a history of first trimester miscarriages that were either known to be chromosomally normal or unknown if aneuploidy existed with progesterone in the luteal phase and during the first trimester. If another loss occurred, and if the fetus showed aneuploidy, I would treat again with just progesterone. If the karyotype was normal or not able to be determined I would add lymphocyte immunotherapy to the progesterone therapy. If despite this duo treatment another spontaneous abortion occurred with a normal karyotype I might then consider IVIG. Of course, the possibility of uterine structural abnormalities and coagulation disorders should also be excluded.

Just because IVIG has theoretical benefits to account for hypotheses of possible immunological imbalances that may lead to fetal rejection does not prove its effectiveness. Even worse than using a very expensive therapy when cheaper options may exist (e.g., progesterone therapy) is an expensive therapy that has no benefit at all. Indeed a recent Cochrane Database Systematic Review did not find that the use of IVIG improved pregnancy outcome in women with a history of recurrent pregnancy loss [9].

One should use caution concerning the conclusions from the aforementioned Cochrane meta-analysis however as there are some flaws in the design of this meta-analysis that could have led to an erroneous inclusion [9]. The most important flaw was not limiting the selection of studies included in the review to women with recurrent pregnancy loss who began IVIG prior to conception rather than after pregnancy was confirmed [9]. In fact in six studies not showing any benefit in preventing another miscarriage in women with recurrent pregnancy loss only the study by Stephenson *et al*. gave IVIG before conception [5, 10-14]. In contrast four of five studies using IVIG preconception found this therapy beneficial [1-5].

Another confounding variable may be the brand of IVIG. Clark *et al*. pointed out that some brands are as much as eight times more potent than others [15]. Interestingly the majority of the negative studies used the less potent brand [15].

I have used IVIG in my practice but because of its expense I could not perform a randomized study or even have enough cases to warrant a matched controlled study. What I can contribute are anecdotes. The most convincing anecdotal case that I treated was one patient who had 12 consecutive losses and had progesterone therapy in her last three. With IVIG she delivered twins successfully in the next pregnancy and delivered twins successfully again with IVIG in her following pregnancy.

Intravenous immunoglobulin also suppresses B-cell production of autoantibody and has been used in women with a history of miscarriages possibly relating to antiphospholipid antibodies [16]. This will be discussed further in a subsequent editorial on coagulation defects and miscarriage.

A possible much less expensive passive immunotherapy treatment for prevention of miscarriage has been proposed and that is the infusion of intralipid [17-20]. Data were published showing suppression of abnormal NK cell activity in peripheral NK cells from women with recurrent miscarriages [21, 22]. There are various hypotheses of how intralipid works but the exact mechanism is not known. A recent study was presented at the 2008 Pacific Coast Reproductive Society by Acacio *et al*. There were 11 women with recurrent pregnancy loss treated by an infusion of 2-4 ml of 20% intralipid solution and ten of these 11 (91%) had a successful pregnancy [23].

These data are encouraging but the numbers are small and uncontrolled. We have tried 4 ml of intralipid infusion for women with a predisposition to miscarriage. Unfortunately, we could not confirm the benefit of intralipid in a matched controlled study. These data were presented at the 2009 American Society for Reproductive Medicine (ASRM) Meeting in Atlanta, Georgia, USA. Possibly women ≤ age 35 could benefit.

At the 2009 ASRM meeting a properly performed multicenter study failed to find benefit for IVIG for recurrent miscarriage.

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Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com